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5.8. Collectively these data clearly indicate that there are important benefits to be expected from intentional weight loss.

5.9. Finally, I note that there is evidence that promoting early rapid weight loss, as might be achieved with compounds such as ephedrine-containing products, is associated with a greater likelihood and amount of long-term weight loss (Astrup & Rossner, 2000).

6. What is the evidence for the efficacy of ephedra and ephedrine containing products?

6.1. Numerous RCTs have been conducted that have examined the efficacy of products containing synthetic ephedrine in combination with caffeine for weight loss. These studies have consistently shown efficacy (c.f., Allison et al., 2001; Coffey et al., in press; Greenway, 2001; Shekelle et al., 2003). Furthermore, the amount of weight lost by subjects taking ephedrine and caffeine in combination has been shown to exceed that offered by prescription medications for weight loss in at least two head-to-head randomized double-blind clinical trials (Breum et al., 1994; Colker & Swain, 2002).

6.2. Multiple studies have also been conducted showing that products containing botanical sources of ephedra alkaloids and caffeine are also effective and, moreover, there is no evidence that they are less effective than products based on synthetic ephedrine and caffeine (Shekelle et al., 2003).

6.3. At least one RCT of an herbal ephedra containing product that contained no caffeine has been conducted (Coffey et al., 2002). Results showed statistically significant efficacy in terms of weight loss.

6.4. Thus, there is a clear and consistent body of evidence supporting the efficacy of ephedrine containing products for weight loss.

7. Is there competent and reliable scientific evidence that ephedra or ephedrine cause or increase the risk of seven events: ischemic stroke, hemorrhagic stroke, seizures, cardiac injury, psychotic injury, primary pulmonary hypertension (PPH), or heat-related injuries (hereafter 'seven events')?

7.1. Regarding terminology, most of the seven events require little interpretation. Exceptions are the phrases "psychotic injury" and "heat-related injury." Going forward, I will take the phrase "psychotic injury" to mean the development or exacerbation of psychosis and the phrase "heat-related injuries" to mean injuries that are at least partially attributed to exposure to high temperatures and result in hospitalization, long-term impairment or disability, or death.

7.2. Given my comments in section 3 above, I have examined the clinical trial literature and the epidemiologic literature for evidence addressing the putative effect of ephedra or ephedrine on risk of each of the seven events.

7.3. I participated in a study of the *Metabolite* product. Safety-related results from this RCT were publicly presented at the 2002 Experimental Biology meeting (Coffey et al., 2002). Of the 279 subjects studied, 92 received the Metabolite product intermittently and 93 received the Metabolite product continuously. Across all 279 subjects, no serious adverse events (and therefore none of the seven events) were reported. I also participated in a second RCT of a product containing ephedrine

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and caffeine with over 100 subjects studied (Coffey et al., in press). Notably, no serious adverse events were observed in any patient. Over the 12-week trial, patients on the active treatment experienced significantly greater weight loss than patients on placebo, without an increase in blood pressure, pulse, or the rate of adverse events.

7.4. The Rand Report (Shekelle et al., 2003), for which I served as a peer-reviewer, reviews pertinent data on this topic. The authors wrote: "*No serious adverse events (e.g., death, myocardial infarction, stroke, etc.) were reported in the 52 clinical trials that reported sample sizes. Therefore, the rate for these adverse events is zero.*" **This clearly indicates that the clinical trials data available do not offer evidence that ephedra or ephedrine cause any of the seven events.**

7.5. With respect to epidemiologic studies of the association of ephedra or ephedrine consumption with the seven events, there is, to the best of my ability to discern, after careful literature search, only one study reported that specifically assesses the association between ephedra or ephedrine consumption and hemorrhagic stroke (Morgenstern et al., 2003) and no studies assessing the association between ephedra or ephedrine consumption and any of the other seven events. The authors wrote "*This case-control study examined the association between Ephedra use and risk for hemorrhagic stroke. For use of Ephedra at any dose during the 3 days before the stroke, the adjusted OR was 1.00 (95% CI 0.32 to 3.11). For daily doses of 32 mg/day, the OR was 0.13 (95% CI 0.01 to 1.54), and for >32 mg/day, the OR was 3.59 (95% CI 0.70 to 18.35).*" It is noteworthy that for neither dose considered was the odds ratio (OR) statistically significant as indicated by the fact that the confidence intervals (CI) include the null value of 1.0. Importantly, in responding to a letter about their paper³, Morgenstern et al wrote "*Our findings...did not indicate an association between use of Ephedra-containing products and risk for hemorrhagic stroke. A trend was observed for the dose over 32 mg per day, and we suggested further investigation was warranted.*" It should also be noted that this study examined only hemorrhagic stroke, not ischemic stroke.

7.6. A Cyrillic-language paper (I read only the English PubMed abstract) conducted what appears to be a small case-control study of stroke among young people (Jovanovic, 1996). The author appears to have studied 150 cases and compared them to an unspecified number of controls or just to general population data. The author wrote "We found no abuse of ephedrine ...as risk factors of stroke in our group..."

7.7. In summation, neither the clinical trial database nor any available epidemiologic studies offer any evidence that consumption of ephedra or ephedrine, either alone or in combination with other ingredients, cause, increase the risk of, or are even associated with the incidence of any of the seven events. I agree with the authors of the Rand Report (Shekelle et al., 2003) when they wrote: "*For rare outcomes, we reviewed case reports, but a causal relationship between ephedra or ephedrine use and these events cannot be assumed or proven....In order to assess a causal relationship between ephedra or ephedrine consumption and serious adverse events, a hypothesis-testing study is needed. Continued analysis of case reports cannot substitute for a properly designed study to assess causality. A case-control study would probably be the study design of choice.*"

8. Specific Commentary on Several Studies Cited by Others as Germane.

³ <http://www.neurology.org/cgi/clatters/60/1/132>

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8.1. Bent et al. (2003a). On superficial inquiry, Bent et al. (2003a) might seem to offer epidemiologic evidence for an association between ephedra/ephedrine and serious adverse events. However, this is not the case. The authors used a combination of poison control report data and sales data to conclude "Products containing ephedra accounted for 64% of all adverse reactions to herbs in the United States, yet these products represented only 0.82% of herbal product sales. The relative risks for an adverse reaction in persons using ephedra compared with other herbs were extremely high, ranging from 100 (95% CI, 83 to 140) for kava to 720 (CI, 520 to 1100) for Ginkgo biloba." There are multiple reasons why this study cannot be taken as competent and reliable evidence that ephedra or ephedrine cause or increase the risk of the seven events.

8.1.1. The study makes no mention of specific serious events such as the seven events considered here, but only talks about an undifferentiated class of adverse events.

8.1.2. The study does not actually involve the sampling of any persons or the recording of any information on them that can be used to control for potential confounding factors. Thus, this is not a well designed, executed, and analyzed study. This is not merely a theoretical concern. As discussed above, obesity itself is a risk factor for many health problems. Therefore, to the extent that people who take ephedra-containing products are more obese, on average, than people taking other herbal products, we might expect them to have more adverse events solely by virtue of their obesity. Similarly if ephedra-containing products are used by people who push themselves to extremes of physical exercise, then the extreme physical exercise alone may account for adverse events. These are just two factors that can be hypothesized to confound the relation between ephedra/ephedrine consumption and adverse events in such a study.

8.1.3. I understand that information provided by the SPINS company that supplied Bent et al the requisite sales data for their analysis indicates that Bent et al's incorporation of information on sales of ephedrine-containing dietary supplements may have been erroneous and lead Bent et al to markedly misestimate the quantities they were trying to estimate. In addition, other concerns have been raised (Anonymous, 2003; Kalman et al., 2003; see Bent et al., 2003b for reply).

8.1.4. As the title of Bent et al's article implies, they can, at best, only look at the relative frequency of adverse event reporting of ephedra compared with other herbal products. Thus, we have no valid control group and, even if there were no other problems with the study, cannot distinguish between an increased frequency of occurrence with ephedra-containing products and a decreased frequency of occurrence with the other herbal products which may occur if, for example, the other products are protective and/or are taken by people with better general health or otherwise healthier lifestyles.

8.2 Walker et al. (submitted). Walker et al. describe results of the *SOPHIA* Study, a study of factors related to primary pulmonary hypertension. The authors collected data on 1335 newly diagnosed pulmonary hypertension patients between January 1998 and June 2001. They stated that "Use of fenfluramines during the past five years was preferentially associated with primary PH versus chronic thromboembolic PH (odds ratio, 8.6; 95% CI: 3.3 to 22.1) and versus precapillary PH due to other causes (odds ratio, 2.7, 95% CI: 1.5 to 4.8). Fenfluramine use was also associated with cases referred but found not to have PH (No-PH). There were unanticipated associations between primary PH and both St. John's Wort and over-the-counter anti-obesity agents containing phenylpropanolamine (PPA)." There are several critical things to consider.

8.2.1. First and foremost, the manuscript makes no mention of the words ephedra or ephedrine at

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any point. At most (and this is questionable – see points 8.2.2 to 8.2.5 below), this study shows an association between use of the categories of 'OTC anti-obesity agents' and 'Any herbal preparations.' However, on page 14 of the Walker et al. manuscript the former category is equated with phenylpropanolamine and it is stated that the latter category is "primarily St. John's wort." Therefore, it is not clear that this study addresses ephedra or ephedrine at all.

8.2.2. Second, according to the authors, the subjects that were referred to the study and found not to have pulmonary hypertension reported the highest rates of anorexigen use which clearly indicates a referral bias (unless one is prepared to believe that anorexigens protect one against developing pulmonary hypertension) and makes the possibility of confounding in this non-randomized study far more plausible.

8.2.3. Third, the study is, at present, unpublished which does not, ipso facto, make it invalid. However, it does mean that it has not survived peer-review and peer-reviewers have not yet had the opportunity to shape the manuscript by asking incisive questions and requiring the authors to answer those questions in the manuscript.

8.2.4. Fourth, many people who take one anti-obesity compound also take or have taken others. Therefore, it is important to control for all other anti-obesity compounds when conducting the statistical analyses to diminish the plausibility of confounding. However, in the statistical models employed, the authors only controlled for one category of other compounds in each analysis. This is an error and leaves open the possibility of residual confounding.

8.2.5. The text implies that Table 3 should contain all pairwise combinations of anorexigen categories. However, not all pairwise combinations are included making one wonder if this is a complete manuscript or a draft still in preparation and requiring checking and completion.

8.2.6. For the reasons described above, this manuscript can, at most, be taken as hypothesis-generating not conclusion-making with respect to any putative effects of ephedra or ephedrine. In fact, two of the authors of the SOPHIA study also authored a recent case report describing a case of PPH in a person that took phenylpropanolamine (Barst & Abenhaim, 2004). The authors concluded "The first case is reported of fatal PAH [i.e., PPH] in a child heavily treated with cold remedies containing phenylpropanolamine, which, in addition to the results of SOPHIA, strengthens the *hypothesis* [emphasis added] that phenylpropanolamine is a risk factor for the development of PAH." Therefore, even these authors consider that the association observed for phenylpropanolamine still only makes it a hypothesis, not a conclusion, that phenylpropanolamine causes PPH. A fortiori, then this applies to any postulated effects of ephedrine that, as far as I can tell from the manuscript, was not directly studied in the Walker et al. (submitted) study.

8.3 Rich et al. (2000). Rich et al (2000) assessed whether there was an association between several different drugs used for weight loss and PPH. Ephedrine and ephedra were not among the compounds studied. Of the compounds studied, only fenfluramine use was associated with PPH. Others such as phentermine were not. This illustrates that not all anorexigens can be considered as a monolithic class with respect to their effects or lack thereof on PPH.

9. Comments on Reports of Other Experts.

I have reviewed the reports of the Plaintiffs' experts and related materials and would like to offer some commentary. I believe that the Plaintiffs' experts make several errors of reasoning and inference and, in a few cases, of fact or communication. I summarize some of the more important

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ones here. In most cases, I do not point out specific expert reports and page numbers that contain these errors, but can do so upon request.

9.1. Errors of Reasoning

9.1.1. Conflating co-occurrence with association. It is widely appreciated that association does not imply causation, but apparently it is less well understood that co-occurrence does not imply association (Adams, 2004). When plaintiffs' experts state that ephedrine or ephedra is associated with something and cite a reference, they are often citing evidence of co-occurrence in the form of one or more case reports, not association. It is important to point out that mere co-occurrence is not evidence of statistical association as defined in section 3.3.3 above and is certainly not evidence of causation.

9.1.2. Misapplication of Hill's guidelines. Several of the plaintiffs' experts misapply Hill's guidelines. Hill (1965) stated "we see that the event B is associated with the environmental feature A, that, to take a specific example, some form of respiratory illness is associated with a dust in the environment. In what circumstances can we pass from this observed association to a verdict of causation? Upon what basis should be proceed to do so?" And, "Our observations reveal an association between two variables, perfectly clear-cut and *beyond what we would care to attribute to the play of chance* [emphasis added]. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?" Clearly, Hill's statements and the very title of his paper show that he intended his 'criteria' to be used only *after an association had been unequivocally demonstrated* to evaluate whether the association was the manifestation of a causal relationship. This is how Hill's criteria were intended by Hill and how they are used in epidemiologic research. Without evidence of association, one has not passed the critical threshold to begin using Hill's criteria. Thus, several experts incorrectly label *co-occurrence* as *association* and then incorrectly try to apply Hill's criteria to ask if the association (that has not been shown to exist) can be construed as causal. It is also noteworthy that with careful reading, it is clear that Hill (1965) intended these as guidelines and not as rigid criteria that will be applicable in all cases. In addition, it must be acknowledged that legitimate questions have been raised about the degree to which they are applicable to modern epidemiology, in which the causes under study may have very modest effects (Phillips & Goodman 2001).

9.1.3. Reliance on anecdotal data (case reports – see point 3.2.4 above). Virtually all of plaintiffs' experts rely heavily on case reports as a basis for their opinions.

9.1.4. Circular Reasoning. Dr. Bent (p. 5) utilizes circular reasoning to conclude that a case of psychosis that occurred in someone taking an ephedrine-containing product was a case of ephedrine-*induced* psychosis on the basis (among other things) that "her case is very similar to other cases of ephedrine/ephedra induced psychosis." In fact, in a recent review related to this topic, Curran et al (2004) wrote "We did not include case series or cross-sectional studies, as these give little information as to the direction of effect or changes over time", concurring with my point 3.2.4 above and Shekelle's statement (quoted in section 3.2.4). Because case reports cannot demonstrate causation or even association, one case report that is purported to demonstrate causation cannot serve as a basis to show that another case report demonstrates causation.

9.1.5. Argumentum Ignorantiam. This refers to a fallacious line of argument in which one contends that a proposition is true on the basis of the fact that there is an absence of evidence to show that it is not true. An example can be found in Dr. Franklin's report (p. 17). Several of the

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plaintiffs' experts point out that (1) certain hypothesized effects of ephedrine or ephedra have not been shown not to exist; (2) Some of the studies that seem to imply that ephedra or ephedrine is safe have flaws and therefore cannot offer conclusive evidence; (3) The available studies and data are limited in their ability to detect particular effects of ephedra or ephedrine if, in fact, such effects exist, due to insufficient statistical power to detect effects on very rare outcomes or other limitations of the available studies. Even if we were to accept points (1), (2), and (3), this would only imply a lack of evidence regarding the safety of ephedra or ephedrine. And a lack of evidence regarding safety cannot be equated with evidence for a lack of safety.

The 'rare event' argument is particularly common. As Shekelle et al. (2003) noted, the clinical trials involving ephedra and ephedrine had finite sample sizes and, therefore, cannot unequivocally rule out conjectured effects of arbitrarily small magnitude. That is, no study can ever unequivocally prove the absence of an effect. The truism that "absence of evidence is not evidence of absence" is well known. It is important to point out that it is no less true that absence of evidence is not evidence of presence. Thus, while the currently available data cannot unequivocally rule out any conjectured effect regardless of how rare the event speculated to be produced is, there are simply no data that demonstrate any effect of ephedrine or ephedra on the seven events.

9.1.6. Appeals to authority. It has been said that "science recognizes no authority." The fact that some person or organization, no matter how august or eminent, holds a certain proposition to be true may capture our attention but does not in and of itself constitute scientific evidence that the proposition is or is not true. Several of the plaintiffs' experts seem to rely on the fact that certain persons, organizations, or textbooks (virtually all cite the same: Goodman & Gilman) state that ephedra or ephedrine may cause a particular serious adverse event as evidence for the truth of the statement. This cannot be taken as scientific evidence.

9.1.7. The Fallacy of Composition. This is an erroneous line of reasoning that can entail drawing a conclusion about a specific member of a class of things based on the fact or belief that some other members of that class have the property. Thus many of plaintiffs' experts discuss effects of anorexigens and state or imply that properties that they attribute to this class will be possessed by all members of this class including ephedra and ephedrine. This is clearly erroneous (see point 3.2.1 above). There are many substances that are anorexigens (things that decrease appetite or food intake) that are never discussed by plaintiffs' experts and for which there is little, if any, reason to even speculate that the substance causes any of the seven events (e.g., the gut peptide cholecystokinin (Moran & Kinzig, 2004)). Clearly, simply because a substance reduces appetite does not mean it will have all of the same properties of all other substances that reduce appetite.

9.1.8. Additional Errors. Plaintiffs' experts frequently rely on studies of other substances, *in vitro* studies, and studies in other species which are not valid bases for conclusions about effects of the substance in question in humans (see section 3.2 above). In fact, if we allowed that such studies were directly relevant, then we also need to consider that in what may be the largest epidemiologic study of an ephedra alkaloid, Porta et al. (1986) showed that pseudoephedrine, a substance closely related to ephedrine and contained in ephedra, did not appear to be associated with any increase risk of serious adverse events and that a large well-controlled study in rodents showed that ephedrine actually increased lifespan in female rats (National Toxicology Program, 1986).

9.2. Errors of Fact, Omission, and Potentially Misinterpretable Statements

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9.2.1. Declaring that there is a consensus in the medical and scientific community that ephedra and ephedrine-containing products are unsafe. Several of plaintiffs' experts opine that such a consensus exists. The writing of some experts such as Dr. Frank Greenway (e.g., Greenway, 2001), clearly indicate that he would not agree with this statement. Robergs et al. (2003) wrote "Numerous medical and/or research trained professionals have expressed their support or opposition to the use of ephedrine. Such debate and conjecture is a good trait of any validation and scientific process, but the diversity of professional opinion on ephedrine is guaranteed to confuse the public about whether ephedrine is safe." Clearly, this diversity of opinion cannot be fairly labeled a consensus. The thousands of comments received by FDA and summarized in Federal Register (FDA, 2004) also illustrate a clear lack of consensus.

9.2.2. Misstatement about serious adverse events. Dr. Buncher states that the "Boozer study identifies serious adverse health consequences experienced by a large number of carefully screened persons ingesting ephedra. Although Dr. Buncher does not explicitly use the phrase "serious adverse event" a reader might be tempted to think that this is what was found. In the biomedical community, the phrase "serious adverse event" is generally defined as "Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse" (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=314.80>). Such events were not reported in the Boozer et al (2001; 2002) studies.

9.2.3. Misstatements regarding relative risks, odds ratios, and fold-increases. Curiously, many of plaintiffs' experts (e.g., Dr. Levine, p. 20; Dr. Bent, p. 2) make the same error of misconstruing odds ratios as relative risks and stating that some risk is X -fold increased when, in fact, the estimate that they are relying on is actually $(X-1)$ -fold. The consistency of their confusion is striking and serves to exaggerate the effects they purport to demonstrate.

9.2.4. Failure to mention that reported point estimates (e.g., of odds ratios) were not statistically significant. Several of plaintiffs' experts cite data, most commonly the data from the Morgenstern et al. (2003) study, as indicative of an association between ephedra or ephedrine consumption and one of the seven events but fail to mention that the estimates were not statistically significant (e.g., Dr. Franklin, p. 19; Dr. Levine, p. 20).

9.2.5. Failure to cite complete information re: Bent et al (2003). Several of plaintiffs' experts cite the paper by Bent et al. (2003), but none cite the follow-up errata and letters to the editor (see section 8.1 above).

9.2.6. Apparent confusion about the nature of case-control and other epidemiologic studies. It appears that several of plaintiffs' experts are confused about the terminology and nature of various epidemiologic designs and how they differ from clinical trials. For example, Dr. Channick (p. 8) states "it would be unethical to perform a prospective, case-controlled [sic] study to determine whether a certain drug caused such a lethal disease." And Dr. Woosley (p. 16) seems to

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think that a case-control study would require that the studied substance be left on the market which is not true given the retrospective nature of case-control studies. Case-control studies are, by definition, not prospective and no subjects are assigned to be exposed to the putative risk factor nor, necessarily, left untreated if suffering from some malady. Therefore, unless Dr. Channick has some ethical perspective that is markedly divergent from that of the mainstream biomedical community, his statements do not stand. There is no reason that a rigorous case-control study could not be done to evaluate whether a putative association between ephedra or ephedrine consumption and some adverse event exists.

10. Summary.

In summation, conjecture has been offered about the putative effects of ephedra or ephedrine on the seven events. Nevertheless, the simple fact remains that there are no clinical trial data or even observational epidemiologic data that show an effect or even an association of ephedra or ephedrine consumption, either alone or in combination with caffeine with any of the seven events in either the general population or any specific subgroup. With respect to risk:benefit balance I have offered substantial data to document the likely benefits of weight loss and an absence of data demonstrating any increased risk of the seven events.

David B. Allison, Ph.D.

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Exhibit A. Curriculum Vita – David B. Allison

[Attached]

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Exhibit B. Materials Reviewed & Referred To

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